4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50, 56, and 812

[Docket No. FDA-2021-N-0286]

RIN 0910-AI07

Protection of Human Subjects and Institutional Review Boards

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is proposing to amend its regulations to modernize, simplify, and enhance the current system for oversight of FDA-regulated human subject research. This proposed rule, if finalized, would harmonize certain sections of FDA's regulations on human subject protection and institutional review boards (IRBs), to the extent practicable and consistent with other statutory provisions, with the revised Federal Policy for the Protection of Human Subjects (the revised Common Rule), in accordance with the 21st Century Cures Act (Cures Act). We believe the proposed changes, if finalized, will reduce regulatory burden on IRBs, sponsors, and investigators. In addition, we propose related changes to the investigational device exemption (IDE) regulations to clarify and update the requirements for the submission of progress reports.

DATES: Either electronic or written comments on the proposed rule must be submitted by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit written comments (including recommendations) on the collection of information under the Paperwork Reduction Act of 1995 by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will

accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and

identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2021-N-0286 for "Protection of Human Subjects and Institutional Review Boards." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the

prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

Submit comments on information collection issues under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at https://www.reginfo.gov/public/do/PRAMain. Find this particular information collection by selecting "Currently under Review - Open for Public Comments" or by using the search function. The title of this proposed collection is "Protection of Human Subjects and Institutional Review Boards--21 CFR Parts 50 and 56 (OMB Control Number 0910-0130)".

FOR FURTHER INFORMATION CONTACT: *With regard to the proposed rule*: Sheila Brown, Office of Clinical Policy, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-6523, Sheila.Brown@fda.hhs.gov.

With regard to the information collection: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

The purpose of this proposed rule is to modernize, simplify, and enhance the current system for oversight of FDA-regulated human subject research. We propose to harmonize certain sections of FDA's regulations on human subject protection (part 50 (21 CFR part 50)) and IRBs (part 56 (21 CFR part 56)), to the extent practicable and consistent with other statutory provisions, with the revised Common Rule,[1] in accordance with section 3023 of the Cures Act

[1] For the purposes of this proposed rule, the phrase "revised Common Rule" refers to the final rule (82 FR 7149, January 19, 2017), modified by the interim final rule that delayed the effective date and general compliance date (83 FR 2885, January 22, 2018) and the final rule that delayed the general compliance date, while allowing use of three

(Pub. L. 114-255, enacted December 13, 2016).[2] The rule also proposes to revise FDA's regulations on IDEs (part 812 (21 CFR part 812)) to clarify and update the requirements for submission of progress reports for clinical investigations of devices. We are also proposing minor technical and editorial changes to the regulations for clarity. FDA believes that these proposed changes, if finalized, would help ensure clarity and enhance both human subject protection and the IRB review process. In addition, harmonizing with the revised Common Rule would reduce regulatory burden for IRBs, sponsors, and investigators.

B. Summary of the Major Provisions of the Proposed Rule

This proposed rule, if finalized, would amend parts 50 and 56 of FDA's regulations. Among other things, we are proposing to: (1) revise the content, organization, and presentation of information included in the informed consent form and process to facilitate a prospective subject's decision about whether to participate in the research; (2) add new basic and additional elements of informed consent; (3) add a provision that would allow IRBs to eliminate continuing review of research in certain circumstances; (4) revise the IRB recordkeeping requirements for certain determinations related to the need for continuing review; and (5) add or modify some definitions. We are also proposing to revise one section of part 812 regarding progress reports submitted by investigators and sponsors to a reviewing IRB for consistency with other revisions we are proposing to the continuing review process in part 56.

C. Legal Authority

The provisions under which FDA is proposing to issue this rule include sections 403, 406, 409, 412, 413, 503, 505, 510, 513-515, 520, 531-539, 541-542, 701, and 721 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 343, 346, 348, 350a, 350b, 353, 355, 360, 360c-360e, 360j, 360hh-360pp, 360rr-360ss, 371, and 379e) and section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

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burden-reducing provisions for certain research during the delay period (83 FR 28497, June 19, 2018).

[2] The term "harmonize," as used in this proposed rule means, "harmonize to the extent practicable and consistent with other statutory provisions," consistent with section 3023 of the Cures Act.

D. Costs and Benefits

The primary quantifiable benefit of the proposed rule is a decreased time burden to IRBs, investigators, and sponsors of clinical trials from increased harmonization with the revised Common Rule. Quantifiable costs include the development of informed consent documents and additional recordkeeping burdens. The estimated annualized cost savings of the proposed rule range from approximately $22 to $103 million in 2018 dollars, with a central estimate of approximately $43 million, discounted at 7 percent over 10 years. At 3 percent, estimates of annualized cost savings range from approximately $22 to $103 million, with a central estimate of approximately $43 million. Estimated annualized costs of the proposed rule range from approximately $0.7 million to $2.3 million, with a central estimate of approximately $1.2 million, discounted at 7 percent. At 3 percent, estimates of annualized costs range from approximately $0.6 million to $2.0 million, with a central estimate of approximately $1.1 million. The impact of the proposed provisions is analyzed in the Preliminary Economic Analysis of Impacts for this proposed rule.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
Cures Act	21st Century Cures Act (Pub. L. 114-255)
FDA	Food and Drug Administration
IRB	Institutional Review Board
FD&C Act	Federal Food, Drug, and Cosmetic Act
FR	Federal Register
HHS	Department of Health and Human Services
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
LAR	Legally Authorized Representative
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PRA	Paperwork Reduction Act of 1995
OMB	Office of Management and Budget
PHS Act	Public Health Service Act
SACHRP	Secretary's Advisory Committee on Human Research Protections
U.S.C.	United States Code
WGS	Whole Genome Sequencing

III. Background

A. Human Subject Protection Requirements Under the Revised Common Rule

The Federal Policy for the Protection of Human Subjects, codified by the Department of Health and Human Services (HHS) at 45 CFR part 46, subpart A, and generally referred to as the Common Rule, sets forth requirements for the protection of human subjects involved in research that is conducted or supported by HHS. The Common Rule was issued in 1991[3] and has been adopted by other Federal Departments and Agencies. The purpose of the Common Rule is to promote uniformity, understanding, and compliance with human subject protections and to create a uniform body of regulations across the Federal Departments and Agencies.[4] On January 19, 2017, HHS announced revisions to modernize, strengthen, and make the Common Rule more effective. The revised Common Rule is intended to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for the regulated community.[5]

B. FDA's Current Regulatory Framework

FDA's regulations for the protection of human subjects at parts 50 and 56 apply to clinical investigations, as defined at current §§ 50.3(c) and 56.102(c), regardless of the source of funding. These regulations, which include requirements for informed consent and IRBs, are intended to protect the rights, safety, and welfare of subjects involved in clinical investigations involving FDA-regulated products.

Prior to the most recent revision to the Common Rule, FDA's regulations regarding the protection of human subjects were largely consistent with the requirements in the Common Rule, with a few exceptions generally arising from differences in FDA's mission or statutory authority. FDA-regulated research that is HHS-conducted or HHS-supported is subject to both HHS's and FDA's regulations. Many IRBs review both types of research and must comply with both sets of

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[3] 56 FR 28001, June 18, 1991.
[4] 80 FR 53933 at 53935, September 8, 2015.
[5] 82 FR 7149, January 19, 2017.

regulations. FDA and the Office for Human Research Protections (OHRP) have been actively working together for many years to harmonize regulatory requirements and guidance.

C. The Cures Act

On December 13, 2016, the Cures Act was signed into law with its purpose of accelerating the discovery, development, and delivery of 21st century cures.[6] Section 3023 of the Cures Act directs the Secretary of HHS, to the extent practicable and consistent with other statutory provisions, to harmonize differences between the HHS Human Subject Regulations and FDA's Human Subject Regulations.[7] Section 3023 of the Cures Act further directs the Secretary of HHS to, as appropriate, make modifications to those regulations, in order to, among other things, reduce regulatory duplication and unnecessary delays. FDA is working with other HHS Agencies in carrying out this statutory mandate, and this proposed rule is being issued in accordance with this provision.

D. Need for the Regulation

As described above, FDA's regulations governing the protection of human subjects largely have been consistent with the requirements of the Common Rule, with a few exceptions generally due to differences in FDA's mission and statutory authority. The revised Common Rule includes provisions intended to strengthen the effectiveness of the human subject protection regulations, and FDA is proposing to harmonize with certain provisions in the revised Common Rule that are applicable to FDA-regulated clinical investigations. For example, proposed new basic and additional elements of informed consent, along with new requirements for the presentation of information in the consent form, would help facilitate a prospective subject's decision about whether to participate in the research and facilitate the enrollment process. In addition, FDA is proposing to harmonize with the revised Common Rule by adding provisions that reduce burden on IRBs and that are intended to allow IRBs to

[6] Pub. L. 114-255.
[7] Pub. L. 114-255, title III, section 3023, December 13, 2016.

focus their resources on research that presents higher risk, thereby enhancing human subject protection. Harmonization will also reduce confusion and regulatory burden for the oversight of studies that are subject to both the revised Common Rule and FDA regulations.

This proposed rule does not address all of the provisions contained in the revised Common Rule. The Agency has addressed some of these provisions in a previously issued proposed rule[8] and is also considering how other provisions of the revised Common Rule that are potentially relevant to FDA-regulated research, such as provisions related to single IRB review for cooperative research, posting of informed consent forms, broad consent, limited IRB review, exempt research, and public health surveillance activities, could be applied to FDA-regulated research. FDA plans to take additional steps to harmonize FDA's regulations with the revised Common Rule, to the extent practicable and consistent with statutory provisions.

IV. Legal Authority

FDA is proposing to issue this rule under the Agency's authority to issue regulations regarding the investigational use of drugs under section 505(i) of the FD&C Act, the investigational use of devices under section 520(g) of the FD&C Act, and the investigational use of biological products under section 351(a) of the PHS Act. In addition, IRB review helps assure the quality and integrity of data from clinical investigations relied upon in submissions to FDA regarding the safety, effectiveness, and/or marketing of FDA-regulated products, including submissions made pursuant to sections 403, 406, 409, 412, 413, 503, 505, 510, 513-515, 520, 531-539, 541-542, and 721 of the FD&C Act and section 351 of the PHS Act. Requirements for informed consent and IRB review also help protect the rights and welfare of human subjects involved in those clinical investigations. Section 701(a) of the FD&C Act authorizes the Agency to issue regulations for the efficient enforcement of the FD&C Act.

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[8] See FDA's notice of proposed rulemaking, "Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations," 83 FR 57378, November 15, 2018 (https://www.govinfo.gov/content/pkg/FR-2018-11-15/pdf/2018-24822.pdf).

These statutory provisions authorize FDA to issue the proposed revisions to its regulations to enhance protection of human subjects and the IRB review process for FDA-regulated clinical investigations.

V. Description of the Proposed Rule

A. 21 CFR Part 50--Protection of Human Subjects

We propose to revise part 50 by adding new requirements, including revised definitions intended to enhance human subject protections. These proposed revisions would require presentation of information in the informed consent document to be in an organized and understandable manner, and to include a concise and focused presentation of the key information most likely to assist a prospective subject in understanding the reasons why the subject might or might not want to participate in the research. The new proposed provisions also include a new basic element of informed consent and three new additional elements of informed consent. New proposed definitions include the definitions of private information, identifiable private information, and identifiable biospecimen. FDA is also proposing to make grammatical corrections or other editorial changes to provide clarity. Table 1 summarizes the proposed changes to part 50 that would harmonize with the revised Common Rule.

Table 1.--Proposed Revisions to Part 50 to Harmonize with the Revised Common Rule

Section No.	FDA Proposes to:	Harmonizes with Revised Common Rule Section (45 CFR part 46)
50.3(l)	Add a sentence to the definition of legally authorized representative (LAR) to address situations in which there is no applicable State or local law governing who may act as a LAR.	46.102(i)
50.3(t)	Add a definition of "written or in writing" that includes both physical and electronic formats.	46.102(m)
50.3(u)	Add a definition of "private information".	46.102(e)(4)
50.3(v)	Add a definition of "identifiable private information".	46.102(e)(5)
50.3(w)	Add a definition of "identifiable biospecimen".	46.102(e)(6)
50.20	Add provisions (d) and (e) for organizing and presenting information about the research to subjects; redesignate or make minor editorial changes to other portions of the paragraph.	46.116(a)(1)-(6)
50.25(a)	Add "or legally authorized representative" to clarify to	46.116(b)

	whom informed consent information must be provided.	
50.25(a)(9)	Add a basic element of informed consent that would require a description of how information or biospecimens may be used for future research or distributed for future research.	46.116(b)(9)
50.25(b)	Add "or the legally authorized representative" to the end of the sentence to clarify to whom informed consent information must be provided.	46.116(c)
50.25(b)(2)	Add "or legally authorized representative's" to clarify that the investigator may terminate the research without the consent of the subject or the LAR.	46.116(c)(2)
50.25(b)(7)-(9)	Add three new additional elements of informed consent, including a statement as to how private information or biospecimens collected during the research may be used for commercial profit and whether the subject will or will not share in this commercial profit, whether clinically relevant results will be disclosed to study subjects, and for research involving biospecimens, whether the research involves whole genome sequencing.	46.116(c)(7)-(9)
50.25(d)	Add a reference to tribal law of American Indian or Alaska Native tribes, to clarify that the reference to "Federal, State, or local law" is intended to include tribal laws; make minor editorial changes.	46.116(i)
50.25(e)	Add a reference to tribal law of American Indian or Alaska Native tribes, to clarify that the reference to "Federal, State, or local law" is intended to include tribal law.	46.116(j)
50.27(a)	Add a parenthetical to provide for consent forms in an electronic format and add "informed consent" before "form."	46.117(a)
50.27(b)(1)	Add "or the subject's legally authorized representative" (to clarify that the subject or LAR shall have the opportunity to read the informed consent form); reorder the sentences and make minor editorial changes.	46.117(b)(1)
50.27(b)(2)	Add a sentence to clarify that when using a short form written informed consent, the key information must be presented first to the subject before other information, if any, is provided, and add "legally authorized representative" in three places; reorder sentences and make minor editorial changes.	46.117(b)(2)

1. Definitions

We propose to harmonize our definition of "legally authorized representative" at § 50.3(l) with the definition in the revised Common Rule at 45 CFR 46.102(i), by adding a sentence to address situations in which there is no applicable State or local law that authorizes a LAR to provide consent on behalf of a prospective research subject. We propose that in these

circumstances, an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context may be considered a LAR for purposes of consenting to the subject's participation in the procedures involved in the research.

In addition, we propose to add several new definitions that are used in the revised Common Rule. At § 50.3(t), we propose to add the definition of "written or in writing," which would harmonize with this definition in the revised Common Rule, at 45 CFR 46.102(m). The definition would include both paper and electronic formats, the latter of which are increasingly used to fulfill many of the documentation requirements that appear throughout FDA's human subject protection regulations. This definition would help clarify that consent forms and related documentation (e.g., written summaries of what is said to subjects and LARs when a short form consent is used in accordance with § 50.27(b)(2) and IRB findings required under § 50.24) may be in an electronic format.

FDA is proposing to add three new definitions for the terms "private information," "identifiable private information," and "identifiable biospecimen." The terms "identifiable private information," and "identifiable biospecimen" and/or references to biospecimens are found in new proposed elements of informed consent at § 50.25(a)(9), (b)(7), and (b)(9), and in the proposed provisions regarding IRB continuing review at § 56.109(g)(1).[9] FDA is proposing to add these new terms and definitions to help modernize our regulations to reflect the changing research landscape involving, for example, access to vast amounts of data from electronic health records and stored biospecimens, the ability to share data and biospecimens for research

[9] We also note that FDA issued a proposed rule on November 15, 2018, that proposed to permit an IRB to approve an informed consent procedure that waives or alters certain informed consent elements or that waives the requirement to obtain informed consent for certain minimal risk studies, when the IRB finds and documents four criteria. The proposed rule invited comment on a fifth criterion for IRB waiver or alteration of informed consent that was added to the revised Common Rule at 45 CFR 46.116(f)(3)(iii) and reads, "if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format" (see 83 FR 57378 at 57381). The comment period on the proposed rule is closed, and FDA is in the process of reviewing comments received on this fifth criterion. If the proposed rule is finalized in a form that includes the fifth criterion, the final provision would include references to "identifiable private information" and "identifiable biospecimen".

purposes, and the development of new technologies and analytic capabilities to advance science and the public health.

We propose to add, at § 50.3(u), a definition of "private information" that harmonizes with the definition of "private information" in the revised Common Rule, at 45 CFR 46.102(e)(4). Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

We propose to add, at § 50.3(v), a definition of "identifiable private information" to harmonize with the revised Common Rule's definition of "identifiable private information" at 45 CFR 46.102(e)(5). We propose to define "identifiable private information" as private information for which the identity of the subject is or may readily be ascertained by the sponsor or investigator or associated with the information. This definition differs from the text of the revised Common Rule provision by including information for which a subject's identity is or may be readily ascertained by the "sponsor" in addition to information that is or may be readily ascertained by the investigator. FDA would consider information for which a subject's identity is or may be readily ascertained by members of the research team conducting the investigation under the supervision of the investigator to be "identifiable private information" under this proposed definition.

FDA's regulations define the terms "sponsor" and "investigator," and they are used throughout our regulations to describe the responsibilities that apply to certain parties involved in FDA-regulated research. OHRP has stated in guidance that it considers the term "investigator" to include "anyone involved in conducting the research,"[10] which is broader than the definition of an "investigator" under FDA's regulations (see, e.g., § 50.3(d)). FDA believes that information

[10] See OHRP's 2008 Guidance, "Coded Private Information or Specimens Use in Research", https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html (accessed January 29, 2021).

for which a subject's identity is or may readily be ascertained by the sponsor of FDA-regulated research should be considered identifiable; and we believe adopting such an approach will help to harmonize the effects of the two sets of regulations.

We propose to add, at § 50.3(w), a definition of "identifiable biospecimen," to harmonize with the revised Common Rule's definition of "identifiable biospecimen" at 45 CFR 46.102(e)(6). For the same reasons described above with respect to the definition of "identifiable private information", we propose to define an identifiable biospecimen as a biospecimen for which the identity of the subject is or may readily be ascertained by the sponsor or investigator or associated with the biospecimen.

The revised Common Rule also includes a provision at 45 CFR 46.102(e)(7)(i) that requires the Federal Departments and Agencies implementing the revised Common Rule, upon consultation with appropriate experts, to reexamine the meaning of the terms "identifiable private information" and "identifiable biospecimen" within 1 year and regularly thereafter (at least every 4 years). That provision further provides that if appropriate and permitted by law, these Federal Departments and Agencies may alter the interpretation of these terms, including through the use of guidance. FDA intends to participate in this effort with HHS and the other Federal Departments and Agencies.

2. General Requirements for Informed Consent

We propose to amend the general requirements for informed consent under § 50.20 to harmonize with the revised Common Rule at 45 CFR 46.116(a)(1) through (6). These requirements address the content, organization, and presentation of information included in the consent form and process to facilitate a prospective subject's decision about whether to participate in the research. To this end, we propose to redesignate our existing requirements as § 50.20(a), (b), (c), and (f) and add new paragraphs (d) and (e). New paragraph (d) would clarify that the prospective subject or the subject's legally authorized representative must be provided

with the information that a reasonable person would want to have to make an informed decision about whether to participate and be given an opportunity to discuss that information.

In new § 50.20(e)(1) and (2), we propose to require that informed consent begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why the subject might or might not want to participate in the research, and that the information be organized and presented in a way that facilitates the subject's or LAR's comprehension.

3. Elements of Informed Consent

We propose to add the phrase "or legally authorized representative" to § 50.25(a) and (b), to harmonize with the revised Common Rule at 45 CFR 46.116(b) and (c), and to clarify to whom informed consent information must be provided.

We propose to add a new basic element of informed consent at § 50.25(a)(9) to harmonize with the revised Common Rule at 45 CFR 46.116(b)(9) and enhance human subject protections. While FDA is not proposing to use language verbatim from the revised Common Rule for this new basic element of informed consent at § 50.25(a)(9), our proposal similarly requires the provision of additional information to potential subjects about the possible future use of their information or biospecimens. This information will help subjects make informed decisions about whether to participate in a particular clinical investigation.

The element of informed consent in the revised Common Rule at 45 CFR 46.116(b)(9) requires that subjects be provided with one of two statements that address research that involves the collection of identifiable private information or identifiable biospecimens.[11] Under the revised Common Rule, identifiers could be removed from information or biospecimens collected as part of a study and the information or specimens could then be used for some secondary

[11] This may be either: (1) a statement that identifiers may be removed from the identifiable private information or identifiable biospecimens, and the information or biospecimens may be used for future research studies or distributed to another investigator for future research studies, without obtaining additional informed consent from the subject or legally authorized representative if this might be a possibility or (2) a statement that the subject's information or biospecimens, even if the identifiers are removed, will not be used or distributed for future research.

research without informed consent or IRB review. The element of informed consent at 45 CFR 46.116(b)(9) would inform subjects of that possibility when applicable.

FDA's proposed new element would require a description of how information or biospecimens may be used for future research or distributed to another investigator for future research. While FDA's proposed element is not limited to the two situations addressed by the statements required under the corresponding element of the revised Common Rule, the research community would be able to develop informed consent forms and processes that comply with both sets of regulations. For example, if appropriate, an investigator may use one of the statements provided in the revised Common Rule to satisfy FDA's proposed requirement. When applicable, an investigator would also be required to provide a description that conveys to subjects the possible future use of their identifiable biospecimens or information that may not be stripped of identifiers.

In addition, as noted above, Congress passed the Cures Act with a stated purpose of accelerating the discovery, development, and delivery of 21st century cures. FDA has been working to modernize its approach to evaluating innovative medical products as new technologies and sources of data create new options for generating and analyzing evidence regarding FDA-regulated products. Such technological advances may have the potential to, for example, streamline and improve the efficiency of clinical studies, but they may also raise new questions in the future about the applicability of certain FDA regulatory requirements, including requirements for informed consent. Therefore, we are concerned about the practicability of limiting this proposed element of informed consent to the two situations addressed by the statements required under the Common Rule at this time. FDA's proposal is intended to incorporate flexibility as to the description that an investigator would provide to each subject or the legally authorized representative to help ensure that subjects are informed regarding possible future uses of information and biospecimens collected from their participation in a clinical investigation as the ways in which information and biospecimens are used relevant to FDA-

regulated products continue to evolve. We request public comment on whether FDA's proposed new basic element of informed consent at § 50.25(a)(9) would provide adequate notice to potential subjects regarding the possible future research use of their information and biospecimens or whether the Common Rule's provision at 45 CFR 46.116(b)(9) would better inform potential subjects about the possible future use of their information and biospecimens in research. We further request public comment on whether the research community anticipates challenges in implementing FDA's proposed new element and whether an alternative approach could lessen such challenges.

FDA is proposing to add three new additional elements of informed consent, § 50.25(b)(7), (8), and (9), to harmonize with the revised Common Rule at 45 CFR 46.116(c)(7), (8), and (9), respectively. Section 50.25(b)(7) would require a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit. Section 50.25(b)(8) would require a statement on whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions. Section 50.25(b)(9) pertains to research involving biospecimens and would require that subjects be informed whether the research will (if known), or might, include whole genome sequencing (WGS). The preamble to the revised Common Rule noted that WGS generates an extremely large amount of information about people, including factors that will contribute to their future medical conditions. The Common Rule goes on to state "Given the unique implications of the information that can be developed through WGS, if it is either known that a specific research study will include this technique, or might include it, we believe that this aspect of the research must be disclosed to prospective subjects as part of the informed consent process."[12] FDA agrees that it is important for prospective subjects to be informed when a clinical investigation involves or may involve WGS, and is, therefore, proposing to add this new element.

[12] 82 FR 7149 at 7216, January 19, 2017.

4. References to Federal, State, or Local Law

We propose to revise § 50.25(d) and (e) by adding a reference to tribal law passed by the official governing body of an American Indian or Alaska Native tribe, to clarify that references to Federal, State, or local law are intended to include tribal law. This proposed change would harmonize FDA regulations with the revised Common Rule at 45 CFR 46.116(i) and (j).

5. Documentation of Informed Consent

We propose to add a parenthetical to § 50.27(a), to clarify that consent forms in an electronic format are an acceptable format and add the term "informed consent" before the term "form" to harmonize the regulatory text with the revised Common Rule at 45 CFR 46.117(a).

We are proposing to revise § 50.27(b)(1) and (2) to include references to a subject's legally authorized representative. We are proposing to reorder sentences and make other changes in § 50.27(b)(1) to clarify that the subject or legally authorized representative shall have adequate opportunity to read the informed consent form. We are proposing to revise § 50.27(b)(2) to require that the key information required by § 50.20 be presented first when using a short form written informed consent. These changes are being proposed to better inform potential subjects about participation in a clinical investigation, and to harmonize with the revised Common Rule at 45 CFR 46.117(b)(1) and (2).

FDA is not proposing to add the new provision found in the revised Common Rule at 45 CFR 46.116(g) at this time. This provision allows IRBs to approve a research proposal for which investigators obtain information or biospecimens without an individual's informed consent for the purpose of screening, recruiting, or determining eligibility of the prospective human subject or LAR if either of the following conditions are met: (1) the investigator will obtain information through oral or written communication with the prospective subject or LAR or (2) the investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

FDA's longstanding policy on preparatory activities to a clinical investigation is that some specific activities are not considered to fall within the definition of a clinical investigation, and therefore do not require IRB review or informed consent under FDA's regulations. For example, we generally have not considered performing a survey of patient records at a site to determine whether the site has a sufficient number of patients with the condition of interest for the clinical investigation to be feasible to require informed consent and IRB review. However, IRB review and informed consent would need to be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for a clinical investigation.[13] We request comment on whether FDA's current policy adequately addresses screening, recruiting, or determining eligibility for an FDA-regulated clinical investigation, or if including the revised Common Rule provision at 45 CFR 46.116(g) would be useful for FDA-regulated clinical investigations. Furthermore, FDA is proposing to make grammatical corrections, updates to statutory references, and other minor editorial changes to part 50. Throughout part 50 a global change has been made to spell out references to "the act", to conform to current *Federal Register* format requirements. Table 2 contains a description of amendments that are unrelated to harmonization with the revised Common Rule.

Table 2.--Proposed Revisions to Part 50 Unrelated to Harmonization with the Revised Common Rule

Section No.	FDA Proposes to:
50.1(a)	Remove specific statutory provisions in final sentence and make minor wording changes.
50.3(b)(20) and 50.3(j)	Update references to certain provisions of the PHS Act.
50.3(b)(16)-(19), (23)	Clarify that citations in this section of the regulatory text are to the FD&C Act.
50.3(i)	Add a sentence to the definition of IRB to state the primary purpose of IRB review is to assure the protection of the rights and welfare of human subjects.
50.24(a)(6)	Revise the citation at the end of the first sentence from "§ 50.25" to "this part" to simplify the regulatory text and ensure that both the informed consent procedures and document are consistent with part 50.
50.25(c)	Add heading to conform to current *Federal Register* format requirements.

[13]See FDA's guidance entitled, "Screening Tests Prior to Study Enrollment, Guidance for Institutional Review Boards and Clinical Investigators," January 1998, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/screening-tests-prior-study-enrollment.

We propose to modify § 50.1(a) to remove the list of statutory provisions in the final sentence because the scope of part 50 is already described in the provision. In addition, removing these provisions will delete certain out of date citations and eliminate the need to update statutory references in the future. Similarly, we propose to modify § 50.3(b)(20) and (j) to remove outdated references to certain provisions of the PHS Act. We propose to clarify that references in § 50.3(b)(16) through (19) and (23) are to sections of the FD&C Act.

We propose to add the following sentence, "The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects" to the definition of "institutional review board" at § 50.3(i), to be consistent with our current definition of IRB at § 56.102(g).

We propose to revise the citation in § 50.24(a)(6) from "§ 50.25" to "this part," to simplify the regulatory text, and to clarify that both the informed consent procedures and documents for studies conducted under § 50.24 must be consistent with part 50.

We also propose to add a heading to § 50.25(c), "Required statement in informed consent documents for applicable clinical trials," to conform to current *Federal Register* format requirements.

B. 21 CFR Part 56--Institutional Review Boards

We propose to revise part 56 to modify provisions related to continuing review, add or modify definitions, and make clarifying editorial changes. FDA believes that these proposed changes will help modernize, clarify, and enhance both human subject protection and the IRB review process. Table 3 identifies sections in which FDA proposes to harmonize our regulatory requirements with language in the revised Common Rule.

Table 3.--Proposed Revisions to Part 56 to Harmonize with the Revised Common Rule

Section No.	FDA Proposes to:	Harmonizes with Revised Common Rule section (45 CFR part 46)
56.102(n)	Add a definition of "written or in writing" that includes both physical and electronic formats.	46.102(m)

56.103(c)	Add a reference to tribal law of American Indian or Alaska Native tribes to clarify that the reference to Federal, State, or local laws is intended to include tribal law; make minor editorial changes.	46.101(f)
56.107(a)	Make minor changes to characteristics of IRB members and the description of categories of subjects who are considered vulnerable.	46.107(a)
56.107(b)	Delete § 56.107(b) because the requirement for IRB membership diversity would be included in § 56.107(a); redesignate remaining sections--see table 4.	46.107(a)
56.108(a)(2)	Move IRB member list details from § 56.115(a)(5) to 56.108(a)(2) and make minor editorial changes.	46.108(a)(2)
56.108(a)(3)(i)-(iii)	Make editorial changes to the requirements for IRB written procedures.	46.108(a)(3)(i), (ii) and (iii)
56.108(a)(4)(i)-(ii), 56.108(b)	Make editorial changes and redesignate the sections.	46.108(a)(4)
56.109(b)	Add "or legally authorized representatives, when appropriate" to clarify that subjects or LARs must be given informed consent information in accordance with § 50.25.	46.109(b)
56.109(c)(3)	Add a new exception to the requirement for documentation of informed consent in specific circumstances.	46.117(c)(1) and (c)(1)(iii)
56.109(d)	Provide that LARs may also receive written statements, if required by the IRB, when documentation of informed consent is waived.	46.117(c)(2)
56.109(f)	Add reference to § 56.109(g).	46.109(e)
56.109(g)	Eliminate the requirement to conduct continuing review of research under certain circumstances.	46.109(f)(1)(iii)
56.110(b)	Remove parenthetical phrase, "(of 1 year or less)".	46.110(b)(1)(ii)
56.111(a)(3)	Revise the description of subjects who may be considered vulnerable.	46.111(a)(3)
56.111(a)(5)	Delete the phrase "and to the extent required" from the requirement to document informed consent in accordance with § 50.27.	46.111(a)(5)
56.111(b)	Revise the description of subjects who are considered vulnerable.	46.111(b)
56.115(a)(3)	Add a requirement to retain records of the rationale for continuing review of research that otherwise would not require continuing review under § 56.109(g).	46.115(a)(3)

1. Definitions

We are proposing to add a new definition, "written or in writing", at § 56.102(n), which would harmonize with the definition in the revised Common Rule at 45 CFR 46.102(m). The new definition would include both paper and electronic formats, the latter of which are increasingly used to fulfill many of the documentation requirements that appear throughout the

IRB and human subject protection regulations. Adding this definition would provide clarity to the regulated community that IRB records may be maintained in electronic formats.

2. Tribal Law and IRB Review

We are proposing to add a reference to tribal law passed by the official governing body of an American Indian or Alaska Native tribe to clarify that the reference to Federal, State, or local laws or regulations, is intended to include tribal law. This proposed revision would also harmonize § 56.103(c) with the revised Common Rule at 45 CFR 46.101(f).

3. IRB Membership

We are proposing to amend § 56.107(a) to harmonize with the revised Common Rule's language at 45 CFR 46.107(a), which describes characteristics of IRB membership. We propose deleting § 56.107(b), which requires IRBs to ensure that their membership not consist entirely of a single gender and prohibits IRB membership from being composed entirely of members of one profession. Section 56.107(b) is no longer necessary because it would be subsumed into proposed § 56.107(a), which would require that an IRB's membership reflects diversity of professional qualifications, and other factors including race, gender, and cultural backgrounds.

4. IRB Functions and Operations

We propose moving the details about IRB membership rosters from § 56.115(a)(5) to § 56.108(a)(2) and making editorial changes to harmonize the language with the revised Common Rule at 45 CFR 46.108(a)(2). We are also proposing editorial and technical revisions to § 56.108, including redesignating some sections, to harmonize with the revised Common Rule.

5. IRB Review of Research

We propose adding "or legally authorized representative, when appropriate" to § 56.109(b), to clarify that subjects or legally authorized representatives must be given informed consent information in accordance with § 50.25, and to harmonize with the revised Common Rule at 45 CFR 46.109(b).

We propose adding new § 56.109(c)(3) to add an exception to the requirement for documentation of informed consent, to harmonize with the revised Common Rule at 45 CFR 46.117 (c)(1)(iii). The new provision would allow the IRB to waive documentation of informed consent for a study that presents no more than minimal risk of harm to the subjects, if the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

We note that the revised Common Rule also retains an exception to the requirement for documentation of informed consent at 45 CFR 46.117(c)(1)(i) for situations in which the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. FDA's regulations historically have not included this same exception, and we are not proposing to add it in this rulemaking because we do not believe it is relevant to FDA-regulated research. We are, however, requesting comment on whether this provision is relevant to FDA-regulated research and any examples of situations when it would be useful.

We propose adding "or legally authorized representatives" to § 56.109(d), to clarify that legally authorized representatives may also receive written statements about the research, if required by the IRB, when documentation of informed consent is waived, and to harmonize with the revised Common Rule at 45 CFR 46.117(c)(2).

We are proposing new § 56.109(g), which would eliminate the requirement for an IRB to conduct continuing review of research, unless an IRB determines otherwise, that has progressed to the point that it involves only data analysis, including analysis of identifiable private information or identifiable biospecimens, and/or accessing followup clinical data from procedures that subjects would undergo as part of clinical care, to harmonize with the revised Common Rule at 45 CFR 46.109(f)(1)(iii). In these circumstances, FDA believes that requiring continuing review would generally not provide added protection to human subjects, and

therefore, would not be necessary. When the only remaining research activities are limited to analysis of data or biospecimens that are part of the IRB-approved study, there is little or no risk to human subjects that would be addressed by requiring continuing review. Furthermore, after all subjects have enrolled and completed the protocol-specified interventions and interactions (including required followup study visits) to support the study's objectives, a protocol may include a long-term followup phase during which subjects continue to be monitored as they undergo clinical care for their medical condition or disease by their healthcare provider. During this continued followup phase, information regarding long-term clinical outcomes may be obtained through accessing clinical data generated during the course of clinical care. This proposed rule would eliminate the requirement for continuing IRB review for this followup portion of the study, unless the IRB determines otherwise.[14] This proposal to eliminate the requirement for continuing IRB review in certain circumstances would apply to FDA-regulated studies that are ongoing on the proposed effective date (see Section VI, Proposed Effective Date below). If any such ongoing studies were federally conducted or supported and also subject to the pre-2018 Requirements (see 45 CFR 46.101(*l*)(1), then the pre-2018 Requirements for continuing review would continue to apply to those studies.

The revised Common Rule contains two other provisions identifying circumstances in which continuing review would not be necessary at 45 CFR 46.109(f)(1)(i) and (ii). We are not proposing to adopt the revised Common Rule provision at 45 CFR 46.109(f)(1)(i), which eliminates the requirement for an IRB to conduct continuing review of research that is eligible for expedited review in accordance with 45 CFR 46.110 unless the IRB determines otherwise. As described below, OHRP has clarified that, in order for research to qualify for expedited review under the current list of research eligible for expedited review referenced in 45 CFR 46.110(a), a determination must still be made by an IRB that the specific circumstances of the

[14] However, FDA would still receive annual reports from sponsors on the progress of such studies in accordance with 21 CFR 312.33 and 812.150(b)(5)).

proposed research involve no more than minimal risk to human subjects. It is not practicable for FDA to adopt this provision because continuing review for minimal risk FDA-regulated clinical investigations would provide meaningful protections to human subjects participating in such investigations. For example, as a study progresses, the analysis of risks to subjects receiving a FDA-regulated product may change based on adverse events that occur during the course of the study and that do not rise to the level of unanticipated problems involving risks to human subjects or otherwise require reporting to the IRB. Continued IRB oversight of such studies would offer added human subject protection to those participating in such investigations by enabling the IRB to assess whether there are any additional risks that present more than minimal risk to participants and require discussion and/or action. Furthermore, for clinical investigations that are subject to both FDA's human subject regulations and the revised Common Rule, the Common Rule provision at 45 CFR 46.109(f)(1)(i) allows an IRB to determine that continuing review of research eligible for expedited review is required.

Finally, we are not proposing to adopt provisions from the revised Common Rule related to limited IRB review at this time, including 45 CFR 46.109(f)(1)(ii). As we continue to consider how other provisions of the revised Common Rule could be applied to FDA-regulated research, including the revised Common Rule's exemptions, we may take additional steps to harmonize with such provisions at a later time.

In addition, as described below, we are proposing changes to the IDE regulations at § 812.150(a)(3) and (b)(5) to align the IRB progress reporting requirements with these proposed changes to IRB continuing review requirements under part 56.

We propose reordering and redesignating the remaining language in § 56.109(f), and current § 56.109(g) and (h) as § 56.109(g), (h), and (i), respectively.

6. Expedited Review

FDA's current regulations under § 56.110(a) state that FDA has established, and published in the *Federal Register*, a list of categories of research that may be reviewed by the

IRB through an expedited review procedure ("expedited review list").[15] FDA is not proposing any changes to § 56.110(a) at this time, and the categories of research included on the expedited review list referenced in § 56.110(a) are identical to the categories of research included on the expedited review list referenced in 45 CFR 46.110(a) ("HHS Expedited Review List").[16] The revised Common Rule requires that the Secretary evaluate the HHS expedited review list at least every 8 years and amend it, as appropriate, after consultation with other Federal Departments and Agencies and after publication in the *Federal Register* for public comment (45 CFR 46.110(a)). We intend to participate in this process and will update our own expedited review list, as appropriate for FDA-regulated studies.

As described in the revised Common Rule, an IRB may use the expedited review procedure to review studies that involve activities appearing on the expedited review list, unless the IRB reviewer determines that the studies involve more than minimal risk (see 45 CFR 46.110(b)(1)(i)). OHRP has clarified that until a new list is finalized, the entire 1998 HHS Expedited Review List, including the "Applicability" section, remains in effect for studies subject to the revised Common Rule.[17] Under the current wording of the "Applicability" section, to be eligible for expedited review research must present no more than minimal risk to subjects. Therefore, application of the 1998 HHS Expedited Review List means that, in order for research to qualify for expedited review under the revised Common Rule, a determination must still be made that the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

Under FDA's current regulations at § 56.110(b)(1), an IRB may use the expedited review procedure to review "[s]ome or all of the research appearing on the list *and* found by the

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[15] See "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure," 63 FR 60353, November 9, 1998.
[16] See "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure," 63 FR 60364, November 9, 1998.
[17] See OHRP, Revised Common Rule Q&As: After January 21, 2019 (the general compliance date for the revised Common Rule), is the 1998 Expedited Review List still in effect for studies subject to the revised Common Rule?, https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/revised-common-rule-q-and-a/index.html (accessed August 6, 2019).

reviewer(s) to involve no more than minimal risk." Because the HHS Expedited Review List, including its "Applicability" section, is still in effect and lists the same categories of research as FDA's expedited review list, IRBs will be able to use the same procedures to review research that may be reviewed via expedited review under the revised Common Rule and FDA's current regulations.

We also note that the current expedited review list (63 FR 60353, November 9, 1998) describes categories of research that include FDA-regulated clinical investigations that may involve more than minimal risk. For example, Category 1 from the current expedited review list describes clinical studies of drugs and medical devices that meet certain conditions, including those that do not require an IND or those for which an IDE application is not required. FDA does not believe that all drug and device studies that do not require an IND or an IDE application qualify as minimal risk. Given this, FDA does not presume all clinical investigations of drugs or medical devices that do not require an IND or an IDE application present no more than minimal risk to subjects. Category 4 also describes clinical studies using medical devices that may not qualify as minimal risk. Therefore, FDA is maintaining the requirement that the reviewer determine that the research involves no more than minimal risk and is only proposing a minor change to the regulatory text in current § 56.110(b) at this time. We propose to remove the parenthetical phrase "(of 1 year or less)" from § 56.110(b)(2) to harmonize with the revised Common Rule at 45 CFR 46.110(b)(1)(ii) because continuing review would not be required in certain circumstances unless the IRB determines otherwise (see § 56.109(g)).

As HHS evaluates and amends, as appropriate, its current expedited review list as described above and as required under 45 CFR 46.110(a), FDA intends to participate in the process and will update our own expedited review list as appropriate and consider if any related changes to our regulations are necessary.

7. Criteria for IRB Approval of Research

We are proposing to add, at § 56.111(a)(3) and (b), updated language consistent with the revised Common Rule, describing categories of subjects who are considered vulnerable to coercion or undue influence, specifically "...children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons." This proposal, if finalized, also would harmonize these sections with the language in the revised Common Rule at 45 CFR 46.111(a)(3) and (b). To simplify our regulatory text, FDA is also proposing to delete the phrase "to the extent required by" from § 56.111(a)(5), so that the requirement would read "Informed consent will be appropriately documented or appropriately waived, in accordance with § 50.27 of this chapter." FDA's proposed revision differs slightly from the revised Common Rule at 45 CFR 46.111(a)(5), which states that informed consent will be appropriately documented or appropriately waived in accordance with 45 CFR 46.117. We are not proposing to include the reference to waiver of documentation as this is addressed under § 50.27.

8. IRB Review of Research

We are proposing to add at § 56.115(a)(3), language that would require the IRB to maintain a record of the rationale for conducting continuing review, if the IRB determines that continuing review of research is necessary (when the research otherwise would not require continuing review under § 56.109(g)). This proposed change would also harmonize the regulations with the language in the revised Common Rule at 45 CFR 46.115(a)(3). The revised Common Rule includes a new recordkeeping requirement at 45 CFR 46.115(a)(8) related to changes made to the regulatory provision at 45 CFR 46.110(b)(1)(i) regarding review of research found on the HHS Expedited Review List. For the reasons described above, FDA is not proposing to make the same change to its expedited review provision at § 56.110(b)(1) and, accordingly, is not proposing to add the related recordkeeping requirement.

We are proposing to revise § 56.115(a)(5) by moving the details about IRB membership rosters from that section to § 56.108(a)(2), to harmonize the language with the revised Common Rule at 45 CFR 46.115(a)(5) and 46.108(a)(2).

Table 4 lists sections that will be moved, redesignated, or divided, with minor editorial changes to the regulatory text in some cases.

Table 4.--Proposed Revisions to Numbering for Regulatory Text in Part 56

Current Section No.	Proposed Revised Section No.
56.107(c)	56.107(b)
56.107(d)	56.107(c)
56.107(e)	56.107(d)
56.107(f)	56.107(e)
56.108	Redesignated to begin with 56.108(a)
56.108(a)(1)	56.108(a)(3)(i)
56.108(a)(2)	56.108(a)(3)(ii)
56.108(a)(3)	56.108(a)(3)(iii)
56.108(b)	56.108(a)(4)
56.108(c)	56.108(b)
56.109(f)	Divided into two sections, 56.109(f) and (h)
56.109(g)	56.109(i)
56.109(h)	56.109(j)

FDA also proposes to make minor changes to the current regulatory text and to delete outdated or unnecessary regulatory text from part 56 (see table 5). In addition, throughout part 56 a global change has been made to spell out references to "the act", to conform to current *Federal Register* format requirements.

Table 5.--Proposed Minor Changes to or Deletion of Regulatory Text in Part 56

Section No.	FDA Proposes to:
56.102(b)(17)	Remove outdated reference to the PHS Act, add corresponding FD&C Act reference.
56.102(l)	Replace outdated references to sections of the PHS Act.
56.103(a)	Delete the reference to 21 CFR part 813, which was removed from FDA's regulations in 1997.
56.109(h) (now 56.109(j))	Delete the second sentence referring to pediatric studies that were ongoing on April 30, 2001, because it is no longer needed.
56.110(b)	Changed reference to § 56.108(c) to § 56.108(b) because of redesignating of sections.
56.110(c)	Changed "which" to "that" in two places.
56.115(a)(6)	Revise the citation to written procedure provisions to reflect redesignating
56.121(c)	Delete "in the *Federal Register*," because notices may now be posted on the FDA website.
56.122	Modify section title from "revocation" to "disqualification," and clarify that disqualification of an IRB is also disclosable to the public.

9. Disqualification of an IRB or Institution

We are proposing to revise § 56.121(c) by deleting the phrase "in the *Federal Register*" from the last sentence. This proposed change would clarify that FDA is not limited to publishing disqualification notices in the *Federal Register* but may use other available and appropriate methods to apprise the public of IRB disqualification actions. For example, FDA now routinely posts such information on the Agency's website.[18]

10. Public Disclosure of Information Regarding Disqualification

We are proposing to revise § 56.122 by modifying the section title to change "revocation" to "disqualification," and clarify that FDA's determination of disqualification of an IRB, as well as an institution, is disclosable to the public under 21 CFR part 20.

C. 21 CFR Part 812--Investigational Device Exemptions

We are proposing to revise § 812.150(a)(3), that requires investigators to submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly. The proposed revisions would provide that such progress reports must be submitted to the reviewing IRB to the extent that continuing review is required by part 56. Elsewhere in this document, FDA is proposing to revise part 56 to eliminate the requirement for IRB continuing review of research under certain circumstances, and FDA does not believe that submission of progress reports to the IRB remains necessary when continuing review of the research by the IRB is not required. This proposed revision to § 812.150(a)(3) is intended to provide consistency between the continuing review requirements under part 56 and the requirements for submission of IDE progress reports to the IRB.

We also propose revising § 812.150(b)(5), which currently provides, among other things, that sponsors must submit progress reports to all reviewing IRBs at regular intervals, and at least yearly. For the same reasons described above regarding § 812.150(a)(3), FDA is proposing to

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[18] https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm.

require sponsors to submit such progress reports to the reviewing IRB to the extent that continuing review is required by part 56. The sponsors of an IDE will continue to submit progress reports to FDA at regular intervals and at least yearly under § 812.150(b)(5), and as may be requested under § 812.150(b)(10), regardless of whether there is continuing IRB review. FDA is proposing to maintain this reporting requirement for continued oversight of investigations that require submission of an IDE application to ensure the Agency receives information regarding the IDE investigation. The proposed rule maintains the requirement that sponsors of treatment IDEs submit semi-annual and annual progress reports to all reviewing IRBs and FDA in accordance with §§ 812.36(f) and 812.150(b)(5).

FDA is not proposing to amend the requirements for treatment IDEs at § 812.36(f), which require semi-annual progress reports to both FDA and the IRB(s) until a marketing application is filed. After filing of a marketing application, § 812.36(f) requires progress reports to be submitted at least annually in accordance with the IDE regulations at § 812.150(b)(5). Our proposed changes to § 812.150(b)(5) would require progress reports to be submitted to reviewing IRBs to the extent that continuing review is required by part 56. As such, after filing of a marketing application, submission of annual progress reports for a treatment IDE to the reviewing IRB would be required only to the extent that continuing review is required under part 56.

VI. Proposed Effective Date

FDA is proposing that the effective date of any final rule that issues based on this proposal would be 180 days from the date of publication of the final rule to allow the regulated community time to prepare to implement the proposed changes. FDA requests comment on this timeframe.

In addition, FDA's goal is to minimize disruption to FDA-regulated studies that are ongoing when the proposed new requirements would become effective, and we are proposing an implementation strategy to address research initially approved by an IRB before the proposed

effective date. For these studies, FDA would not intend to enforce compliance with the following proposed provisions:

- proposed new § 50.20(d) through (e), which would, among other things, require informed consent to begin with a concise and focused presentation of "key information" and would require informed consent information to be organized and presented in certain ways;
- the proposed new basic and additional elements of informed consent at § 50.25(a)(9) and (b)(7) through (9); and
- the proposed revision to § 50.27(b)(2), which would require the key information required by § 50.20 to be presented first to the subject or the subject's legally authorized representative when informed consent information is provided orally and documented using a short form.

This approach reflects FDA's concern that, for research an IRB has approved before the proposed effective date, revising the already approved informed consent form and process to comply with the provisions identified above could cause unwarranted burden and, in some cases, delay research. However, nothing in this proposal would prevent sponsors and investigators from updating the consent forms for research that was approved before the proposed effective date to comply with the above-listed provisions. We request comment on this proposed approach.

VII. Preliminary Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts;

and equity). This proposed rule has been designated an economically significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because estimated cost savings of the proposed rule are greater in magnitude than estimated costs, and because we do not expect the effects of the rule to affect entities by size, we propose to certify that the rule, if finalized, will not have a significant economic impact on a substantial number of small entities. However, as discussed in the Preliminary Economic Analysis of Impacts (Ref. 1), there is a lack of high quality, comprehensive data regarding the number of small and very small institutions associated with IRBs, as defined by revenue. We have prepared an initial regulatory flexibility analysis and are seeking comment on the data and assumptions used in that analysis.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $158 million, using the most current (2020) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

If finalized, the proposed rule would: (1) revise content, organization, and presentation of the information included in the informed consent form and process to facilitate a prospective subject's decision about whether to participate in a clinical investigation; (2) add new basic and additional elements of informed consent; (3) add a provision allowing IRBs to eliminate continuing review of some research; (4) revise IRB recordkeeping requirements for certain determinations related to the need for continuing review; and (5) add or modify some definitions.

The rule also proposes to revise FDA's regulations IDEs (part 812) to clarify and update the requirements for submission of progress reports for clinical investigations of devices.

The proposed rule would harmonize certain aspects of FDA's regulations on IRBs and informed consent processes, to the extent practicable and consistent with statutory provisions, with the requirements of the revised Common Rule in accordance with section 3023 of the Cures Act. The proposed rule should reduce the costs of conducting clinical investigations by harmonizing informed consent and certain continuing review processes for FDA-regulated research with the revised Common Rule. The proposed rule will also generate costs that we estimate will be relatively smaller than expected cost savings in the form of additional time spent learning the rule, developing new informed consent documents in line with the rule, and revised recordkeeping requirements related to continuing review. We also expect qualitative benefits that we do not estimate explicitly due to data limitations, including increased efficiency of clinical investigations and medical product development and improved human subject knowledge by providing subjects with clearer clinical investigation information. Table 6 summarizes our estimates of the annualized costs and annualized benefits (in the form of cost savings) of the proposed rule.

The benefits of the proposed rule take the form of quantified net cost savings (cost savings minus costs) and qualitative benefits. We estimate that the benefits of the proposed rule are approximately $68 million annually in 2018 dollars, with a lower bound of approximately $22 million and an upper bound of approximately $249 million, discounted at 7 percent over 10 years. When discounted at 3 percent, estimated benefits are approximately $68 million annually, with a lower bound of approximately $22 million and an upper bound of approximately $249 million. We also expect quantitative benefits in the form of cost savings from increased efficiency in medical product innovation and in the form of improved human subject knowledge. We estimate that the costs of the proposed rule are approximately $1.4 million annually in 2018 dollars, with a lower bound of approximately $0.7 million and an upper bound of approximately

$3.0 million, discounted at 7 percent over 10 years. When discounted at 3 percent, estimated costs are approximately $1.3 million annually, with a lower bound of approximately $0.6 million and an upper bound of approximately $2.6 million. These estimates are summarized in table 6.

Table 6.--Summary of Benefits, Costs and Distributional Effects of Proposed Rule (millions$)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year	$68	$22	$249	2018	7%	10 years	Benefits are Cost Savings
		$68	$22	$249	2018	3%	10 years	Benefits are Cost Savings
	Annualized Quantified					7%		
						3%		
	Qualitative	Increased efficiency in medical product innovation and improved human subject knowledge by providing subjects with clearer information regarding clinical investigations						
Costs	Annualized Monetized $millions/year	$1.4	$0.7	$3.0	2018	7%	10 years	
		$1.3	$0.6	$2.6	2018	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: Small Business: Wages: Growth:							

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 1) and at https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521). A description of these provisions is given in the *Description* sections of this document with an estimate of the recordkeeping and third-party disclosure burden associated with the proposed rule. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

A. Protection of Human Subjects and Institutional Review Boards--Parts 50 and 56 (OMB Control Number 0910-0130)

Description: Provisions in part 50 provide for the protection of human subjects involved in FDA-regulated clinical investigations. Provisions in part 56 set forth requirements for the composition, operation, and responsibilities of an IRB. IRBs serve in an oversight capacity by reviewing, among other things, informed consent documents and protocols for FDA-regulated studies to make findings required to approve research and document IRB actions. If finalized,

the proposed rule would revise FDA's current regulations in parts 50 and 56 related to informed consent, waiver of documentation of informed consent, and IRB continuing review.

1. Proposed Changes to Informed Consent Requirements (part 50)

Under FDA's existing regulations at part 50, investigators must obtain informed consent of subjects or their LARs before involving subjects in an FDA-regulated clinical investigation, typically through written consent forms reviewed and approved by an IRB and signed by the subject or LAR. FDA's current regulations at §§ 50.23 and 50.24 provide for exceptions from the requirement to obtain informed consent in certain narrow circumstances. The information collections associated with development, IRB approval, and documentation of informed consent in compliance with FDA's existing regulations at §§ 50.25 and 50.27 are currently approved under OMB control number 0910-0130.

The proposed rule, if finalized, would revise provisions at §§ 50.20, 50.25, and 50.27 regarding the content, organization, and presentation of information in the informed consent. Proposed § 50.20(e) would require informed consent to begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of informed consent would have to be organized and presented in a way that facilitates comprehension. The proposed rule would also add a new basic element of informed consent at proposed § 50.25(a)(9) and three new additional elements of informed consent at proposed § 50.25(b)(7) through (9). Finally, the proposed rule would revise § 50.27(b)(2) to clarify that when a short form is used to document that the required elements of informed consent have been presented orally to the subject or LAR, the key information required by proposed § 50.20 must be presented first to the subject or LAR. These proposed changes to FDA's informed consent requirements would help ensure that prospective subjects receive and understand information important to choosing whether to participate in a clinical investigation.

2. Proposed Changes to Requirements for IRB Waiver of Documentation of

FDA's existing regulations at § 56.109(c) provide for an IRB to waive the requirements for documentation of informed consent in some circumstances. To harmonize with the revised Common Rule, proposed § 56.109(c)(3) would allow an IRB to waive documentation of informed consent in an additional circumstance: if the IRB finds that the research presents no more than minimal risk of harm to the subjects, the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, and there is an appropriate alternative mechanism for documenting that informed consent was obtained. IRBs are already required to maintain adequate documentation of their activities under FDA regulations at § 56.115, including minutes of IRB meetings and records of continuing review activities. Those existing recordkeeping requirements are part of the information collection currently approved under OMB control number 0910-0130. We believe that proposed § 56.109(c)(3) represents an unusual circumstance that would affect a limited number of IRBs and thus introduce minimal change in burden associated with IRB recordkeeping.

FDA is also proposing changes to its requirements for continuing review to harmonize with the revised Common Rule, which are intended to reduce burden on IRBs and allow them to focus their resources on research that presents higher risk. Under proposed § 56.109(g), unless an IRB determines otherwise, continuing review of research is not required for research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study: (1) data analysis, including analysis of identifiable private information or identifiable biospecimens or (2) accessing followup clinical data from procedures that subjects would undergo as part of clinical care. In these circumstances, FDA believes that requiring continuing review would generally not provide added protection to human subjects, and, therefore, would not be necessary. If an IRB chooses to conduct continuing review for research that meets these criteria, the rationale for doing so must be documented according to proposed § 56.115(a)(3).

Description of Respondents: Respondents to the information collections include investigators that develop written informed consent materials for submission to an IRB and that present this informed consent information to subjects participating in FDA-regulated clinical investigations (table 7) and IRBs that review and approve FDA-regulated clinical investigations (table 8).

We estimate the burden of the information collection as follows:

Table 7.--Estimated Third-Party Disclosure Burden[1]

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
50.20(e), 50.25, and 50.27--development of written consent materials for submission to IRB	4,122	1	4,122	2.5	10,305
50.25 and 50.27--disclosure of consent information to subjects	4,122	200	824,400	0.5 (30 minutes)	412,200
Total					422,505

[1] There are no capital or operating and maintenance costs associated with the information collection.

Based on our review of information from ClinicalTrials.gov (https://clinicaltrials.gov/; accessed on March 8, 2018), we estimate that there are 4,122 new FDA-regulated clinical investigations per year. Table 7, row 1 provides our estimate of the annual burden respondents will incur for developing written consent materials for new clinical investigations. We do not anticipate that investigators will revise informed consent forms and processes to reflect the proposed revisions to §§ 50.20(e), 50.25, and 50.27 for ongoing clinical trials that are approved by an IRB before the proposed effective date of the rule, and therefore, our estimate reflects burden we attribute to new clinical investigations. If the proposed rule is finalized, we estimate that for each new clinical investigation, one investigator will spend a total of 2.5 hours to develop written consent materials to submit for IRB approval in connection with a new clinical investigation to satisfy proposed and existing requirements under §§ 50.20(e), 50.25, and 50.27

(table 7, row 1), including existing requirements already accounted for under OMB control number 0910-0130. This new total estimated time includes 0.5 hours for developing a written informed consent form or the written summary of what is said to the subject as required under § 50.27(b)(2) in order to comply with the proposed new requirements at §§ 50.20(e), 50.25(a)(9) and (b)(7) through (9), and 50.27(b)(2).

The information collection approved under OMB control number 0910-0130 pertains to developing and documenting informed consent in accordance with §§ 50.25 and 50.27 and includes burden attributable to development and approval by an IRB of a site-specific informed consent document, and the documentation of informed consent, but does not currently account for subsequent presentation of the informed consent information to subjects. We address this third-party disclosure in table 7, row 2, and seek its inclusion under control number 0910-0130, to ensure clarity regarding the PRA approval status of the presentation of informed consent information to individual subjects in all FDA-regulated clinical investigations to which §§ 50.25 and 50.27 apply. Our ability to provide a precise estimate for this burden is limited by the significant variability in the size of clinical investigations, which can range from a few subjects to tens of thousands, and which thus affects the estimated average number of responses per respondent. In accordance with PRA regulations (5 CFR 1320 at 1320.8(b)(3)(iii)), we provide our estimate in table 7, row 2 of the annual average burden and invite comment on this estimate.

Table 8.--Estimated Annual Recordkeeping Burden[1]

21 CFR section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
56.109(c)(3)--Waiver of documentation of informed consent when subjects are members of a distinct cultural group in which signing forms is not the norm, research is no more than minimal risk, and appropriate mechanism for documenting that informed consent was obtained	25	1	25	0.25 (15 minutes)	6.25
56.115(a)(3)--Documentation of rationale when conducting continuing review of research that otherwise would not require continuing review	500	1	500	0.25 (15 minutes)	125

Total					131.25

[1] There are no capital or operating and maintenance costs associated with the information collection.

We estimate that one percent of IRBs (25) will review one study annually to determine whether the subjects or their LARs are members of a distinct cultural group or community in which signing forms is not the norm, such that the IRB may waive documentation of informed consent under proposed § 56.109(c)(3). We believe these IRBs are likely to document the findings required to approve the waiver in IRB meeting minutes (§ 56.115(a)(2)), although they could be documented elsewhere in IRB records. We estimate that this recordkeeping will require 15 minutes to complete, as reflected in table 8, row 1.

We estimate that 500 IRBs will review one study annually that will be subject to the proposed requirement under § 56.115(a)(3) to document the IRB's rationale for conducting continuing review of research that otherwise would not require continuing review under proposed § 56.109(g). We estimate that the associated documentation will require 15 minutes to complete, as reflected in table 8, row 2.

B. Investigational Device Exemptions--Part 812 (OMB Control Number 0910-0078)

Description: Provisions in part 812 set forth procedures for the conduct of clinical investigations of devices and provide for the protection of human subjects involved in such investigations. Under FDA's existing regulations at § 812.150(a)(3) and (b)(5), sponsors and investigators of device investigations are required, among other things, to submit progress reports to reviewing IRBs at regular intervals, but in no event less often than yearly. The proposed rule would revise § 812.150(a)(3) and (b)(5) to require that such progress reports on clinical investigations of devices be submitted to the reviewing IRB to the extent that continuing review is required by part 56. Therefore, the proposed change would eliminate the need to submit progress reports to the reviewing IRB for non-significant risk and significant risk device studies when continuing review is no longer required under part 56. The proposed revisions to

part 812 are intended to provide consistency between the proposed continuing review requirements under part 56 and the requirements for submission of IDE progress reports to IRBs.

Description of Respondents: Respondents to the information collection are investigators for and sponsors of clinical investigations of devices.

Table 9.--Estimated Annual Third-Party Disclosure Burden Under 21 CFR part 812[1]

21 CFR Part 812; IDEs	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
812.150; reports for non-significant risk studies	1	1	1	6	6

[1] There are no capital or operating and maintenance costs associated with the information collection.

We characterize burden associated with progress reports under § 812.150 that are submitted from clinical investigators and sponsors to reviewing IRBs as a disclosure burden. As noted above, the proposed changes to § 812.150(a)(3) and (b)(5) would eliminate the need to submit progress reports to reviewing IRBs for non-significant risk and significant risk devices studies when continuing review is no longer required under part 56. Therefore, there is no additional burden, and FDA believes these proposed changes may reduce the number of progress reports submitted to reviewing IRBs for device studies that progress to a point where continuing review is no longer required.

We maintain our current estimate of one report annually for non-significant risk device studies that do not require submission of an IDE application to FDA, and that preparing the report requires 6 hours, as approved under OMB control number 0910-0078. We note however, this is a longstanding estimate and invite comment specifically with regard to the number of progress reports sponsors and investigators anticipate submitting annually to reviewing IRBs and the burden associated with progress reports under § 812.150 for non-significant risk studies. We do not specifically estimate burden for progress reports to reviewing IRBs for significant risk studies under OMB control number 0910-0078 and therefore invite comment here on how, if at all, the proposed changes would affect the number of progress reports sponsors and investigators

anticipate submitting annually to reviewing IRBs and overall burden for these significant risk studies.

To ensure that comments on information collection are received, OMB recommends that written comments be submitted through https://www.reginfo.gov/public/do/PRAMain (see ADDRESSES). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the *Federal Register*.

X. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XII. Reference

The following reference is on display at the Dockets Management Staff (see ADDRESSES) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at https://www.regulations.gov. FDA has verified the website address, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA, Preliminary Economic Analysis of Impacts, Docket No. FDA-2021-N-0286, available at https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.

List of Subjects

21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 56

Human research subjects, Reporting and recordkeeping requirements, Safety.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 50, 56, and 812 be amended as follows:

PART 50--PROTECTION OF HUMAN SUBJECTS

1. The authority citation for part 50 is revised to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 360hh-360pp, 360rr-360ss, 371, 379e, 381; 42 U.S.C. 216, 241, 262.

2. In part 50, remove the words “the act” and add in their place “the Federal Food, Drug, and Cosmetic Act” wherever they appear.

3. In § 50.1, revise the last sentence of paragraph (a) to read as follows:

§ 50.1 Scope.

(a) * * * Compliance with these parts is intended to protect the rights and safety of human subjects involved in such investigations.

* * * * *

4. In § 50.3:

a. Remove and reserve paragraph (a);

b. Amend paragraphs (b)(16) through (19) by adding "of the Federal Food, Drug, and Cosmetic Act" at the end of each sentence;

c. Amend paragraph (b)(20) by removing "section 358 of the Public Health Service Act" and adding in its place "section 534 of the Federal Food, Drug, and Cosmetic Act";

d. Revise paragraphs (i), (j), and (l); and

e. Add paragraphs (t) through (w).

The revisions and additions read as follows:

§ 50.3 Definitions.

* * * * *

(i) *Institutional review board (IRB)* means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, and to approve the initiation of and conduct periodic review of such research. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the Federal Food, Drug, and Cosmetic Act.

(j) *Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act or under section 351 of the Public Health Service Act (42 U.S.C. 262).

* * * * *

(l) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

* * * * *

(t) *Written or in writing* means writing on a tangible medium (e.g., paper) or in an electronic format.

(u) *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

(v) *Identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the sponsor or investigator or associated with the information.

(w) *Identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the sponsor or investigator or associated with the biospecimen.

5. Revise § 50.20 to read as follows:

§ 50.20 General requirements for informed consent.

Except as provided in §§ 50.23 and 50.24:

(a) Before involving a human subject in research covered by these regulations, the investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.

(b) An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and

consider whether or not to participate and that minimize the possibility of coercion or undue influence.

(c) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.

(d) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

(e)(1) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

(2) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

(f) No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

§ 50.24 [Amended]

6. In § 50.24, in paragraph (a)(6), remove "§ 50.25" at the end of the first sentence and add in its place "this part".

7. In § 50.25:

a. Revise paragraphs (a) introductory text and (a)(3);

b. Add paragraph (a)(9);

c. Revise paragraphs (b) introductory text and (b)(1), (2), and (5);

d. Add paragraphs (b)(7) through (9);

e. Add a heading to paragraph (c); and

f. Revise paragraphs (d) and (e).

The additions and revisions read as follows:

§ 50.25 Elements of informed consent.

(a) *Basic elements of informed consent*. In seeking informed consent, the following information shall be provided to each subject or legally authorized representative:

* * * * *

(3) A description of any benefits to the subject or to others that may reasonably be expected from the research.

* * * * *

(9) A description of how information or biospecimens may be used for future research or distributed to another investigator for future research.

(b) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject or legally authorized representative:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or legally authorized representative's consent.

* * * * *

(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.

* * * * *

(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

(c) *Required statement in informed consent documents for applicable clinical trials.* * * *

(d) *Preemption.* The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that require additional information to be disclosed in order for informed consent to be legally effective.

(e) *Emergency medical care.* Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe).

8. Revise § 50.27 to read as follows:

§ 50.27 Documentation of informed consent.

(a) Except as provided in § 56.109(c) of this chapter, informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated (including in an electronic format) by the subject or the subject's legally authorized representative at the time of consent. A written copy shall be given to the person signing the informed consent form.

(b) Except as provided in § 56.109(c) of this chapter, the consent form may be either of the following:

(1) A written informed consent form that meets the requirements of this part. The investigator shall give either the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative.

(2) A short form written informed consent form stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. The key information required by § 50.20 must be presented first to the subject or the subject's legally authorized representative, before other information, if any, is provided. The IRB shall approve a written summary of what is to be said to the subject or the legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the subject's legally authorized representative, in addition to a copy of the short form.

PART 56--INSTITUTIONAL REVIEW BOARDS

9. The authority citation for part 56 continues to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h, 360i, 360j, 360hh-360ss, 371, 379e, 381; 42 U.S.C. 216, 241, 262.

10. In part 56, remove the words "the act" and add in their place "the Federal Food, Drug, and Cosmetic Act".

11. In § 56.102, remove and reserve paragraph (a), revise paragraphs (b)(17) and (l), and add paragraph (n).

The revisions and addition read as follows:

§ 56.102 Definitions.

* * * * *

(b) * * *

(17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 534 of the Federal Food, Drug, and Cosmetic Act.

* * * * *

(l) *Test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act or under section 351 of the Public Health Service Act (42 U.S.C. 262).

* * * * *

(n) *Written or in writing* means writing on a tangible medium (e.g., paper) or in an electronic format.

12. In § 56.103, revise paragraphs (a) and (c) to read as follows:

§ 56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§ 56.104 and 56.105, any clinical investigation that must meet the requirements for prior submission (as required in parts 312 and 812 of this chapter) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

* * * * *

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects.

13. Revise § 56.107 to read as follows:

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects.

(b) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(c) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(d) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(e) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

14. Revise § 56.108 to read as follows:

§ 56.108 IRB functions and operations.

(a) In order to fulfill the requirements of these regulations, each IRB shall:

(1) [Reserved]

(2) Prepare and maintain a current list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution, for example, full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant;

(3) Establish and follow written procedures for:

(i) Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(ii) Determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;

(iii) Ensuring prompt reporting to the IRB of proposed changes in a research activity; and for ensuring that investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject.

(4) Establish and follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:

(i) Any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; and

(ii) any suspension or termination of IRB approval.

(b) Except when an expedited review procedure is used (as described in § 56.110), an IRB must review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

15. In § 56.109:

a. Revise paragraph (b);

b. Add paragraph (c)(3);

c. Revise paragraphs (d) and (f);

d. Redesignate paragraphs (g) and (h) as paragraphs (i) and (j), respectively;

e. Add new paragraphs (g) and (h); and

f. Revise newly redesignated paragraphs (i) and (j).

The revisions and additions read as follows:

§ 56.109 IRB review of research.

* * * * *

(b) An IRB shall require that information given to subjects or legally authorized representatives, when appropriate, as part of informed consent is in accordance with § 50.25 of this chapter. The IRB may require that information, in addition to that specifically mentioned in § 50.25 of this chapter, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) * * *

(3) The IRB may waive documentation of informed consent if it finds that the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects, and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) or (3) of this section, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

* * * * *

(f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, except as described in paragraph (g) of this section.

(g) Unless an IRB determines otherwise, continuing review of research is not required for research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

(1) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

(2) Accessing followup clinical data from procedures that subjects would undergo as part of clinical care.

(h) An IRB shall have authority to observe or have a third party observe the consent process and the research.

(i) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under § 50.24 of this chapter a copy of information that has been publicly disclosed under § 50.24(a)(7)(ii) and (iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

(j) When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research.

16. In § 56.110, revise paragraphs (b) and (c) to read as follows:

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

* * * * *.

(b)(1) An IRB may use the expedited review procedure to review either or both of the following:

(i) Some or all of the research appearing on the list described in paragraph (a) of this section and found by the reviewer(s) to involve no more than minimal risk;

(ii) Minor changes in previously approved research during the period for which approval is authorized.

(2) Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in § 56.108(b).

(c) Each IRB that uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals that have been approved under the procedure.

* * * * *

17. In § 56.111, revise paragraphs (a)(1), (3), and (5) through (7) and (b) to read as follows:

§ 56.111 Criteria for IRB approval of research.

(a) * * *

(1) Risks to subjects are minimized:

(i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk and

(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

* * * * *

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

* * * * *

(5) Informed consent will be appropriately documented or appropriately waived, in accordance with § 50.27 of this chapter.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

* * * * *

18. In § 56.115, revise paragraphs (a)(3), (5), and (6) and (b) to read as follows:

§ 56.115 IRB records.

(a) * * *

(3) Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in § 56.109(g).

* * * * *

(5) A list of IRB members in the same detail as § 56.108(a)(2).

(6) Written procedures for the IRB as required by § 56.108(a)(3) and (4).

* * * * *

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research. The institution or IRB may maintain the records in printed form or electronically. All records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

* * * * *

19. In § 56.121, revise the last sentence in paragraph (c) to read as follows:

§ 56.121 Disqualification of an IRB or an institution.

* * * * *

(c) * * * In addition, the Agency may elect to publish a notice of its action.

* * * * *

20. Revise § 56.122 to read as follows:

§ 56.122 Public disclosure of information regarding disqualification.

A determination that FDA has disqualified an IRB or an institution and the administrative record regarding that determination are disclosable to the public under part 20 of this chapter.

PART 812--INVESTIGATIONAL DEVICE EXEMPTIONS

21. The authority citation for part 812 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 360hh-360pp, 360rr-360ss, 360bbb-8b, 371, 372, 374, 379e, 381, 382; 42 U.S.C. 216, 241, 262.

22. In § 812.150, revise paragraphs (a)(3) and (b)(5) to read as follows:

§ 812.150 Reports.

(a) * * *

(3) *Progress.* An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly. Such progress reports shall be submitted to the reviewing IRB to the extent that continuing review is required by part 56 of this chapter.

* * * * *

(b) * * *

(5) *Progress reports*. At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRBs. Such progress reports shall be submitted to reviewing IRBs to the extent that continuing review is required by part 56 of this chapter. In the case of a significant risk device, a sponsor shall submit progress reports to FDA at regular intervals, and at least yearly. A sponsor of a treatment IDE shall submit semiannual progress reports to all reviewing IRBs and FDA in accordance with § 812.36(f) and annual progress reports in accordance with this section.

* * * * *

Dated: September 23, 2022.

Robert M. Califf,

Commissioner of Food and Drugs.

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